Project Details	
Project Code	NMH27Br Corey
Title	Molecular basis of CASK mutations and their role in neural development
Research Theme	Neuroscience & Mental Health
Project Type	Other
Summary	This interdisciplinary PhD project will investigate how disease-causing mutations alter the structure and function of CASK, a key protein required for synaptic development, neuronal communication, and brain function. Mutations in CASK cause severe neurodevelopmental disorders, including intellectual disability and microcephaly. The student will combine cutting-edge AI-based protein structure prediction tools, including AlphaFold3, with advanced structural bioinformatics to analyse pathogenic variants, uncover mechanisms of disease, and develop methods for prioritising clinically relevant mutations. The project offers training in AI, computational biology, and neuroscience, providing highly transferable skills for careers in academia, biotechnology, and biomedical research.
Description	CASK is a highly conserved, multi-domain scaffolding protein that plays essential roles in synaptic development, neuronal communication, and brain formation. It coordinates the assembly of large protein complexes containing interaction partners such as neurexins, syndecans, and ion channels, which are critical for establishing and maintaining functional neural circuits. Disruption of these molecular networks can have profound consequences for nervous system development and function. Pathogenic variants in CASK are associated with a spectrum of severe X-linked neurodevelopmental disorders, including X-linked intellectual developmental disorder (XLID), with or without nystagmus and FG syndrome (OMIM: 300422), X-linked optic and ophthalmic problems, and intellectual developmental disorder and microcephaly with pontine and cerebellar hypoplasia (MICPCH) (OMIM: 300749). Disease causing variants include loss-of-function mutations, splice-site alterations, and missense changes that can reduce CASK abundance, impair protein interactions, and disrupt the assembly of synaptic signalling complexes. Despite growing clinical recognition of CASK-associated disorders, the molecular mechanisms underlying many disease-causing variants remain poorly understood. This interdisciplinary PhD project will combine artificial intelligence, structural biology, genetics, and functional genomics to investigate how pathogenic mutations alter CASK structure and function. Working with Drs Robin Corey and Amber Knapp-Wilson, the student will apply state-of-the-art AI-driven molecular modelling tools, including AlphaFold3, together with advanced structural bioinformatics approaches to predict the effects of disease-associated variants on protein stability, dynamics, and molecular interactions. These analyses will form the basis of a variant-prioritisation framework designed to identify mutations most likely to have significant functional consequences. The highest-priority variants will then be tested experimentally. In Prof Hodge's laboratory, the student will introduce selected mutations into Drosophila models and assess their effects on behaviour and neurological function. In collaboration with Prof Ben Housden, they will

	use functional genomics approaches to determine how CASK dysfunction alters gene expression and cellular pathways. Together, these studies will provide mechanistic insight into how molecular defects propagate to changes in cells, tissues, and whole-organism phenotypes. A further objective of the project is to identify previously unrecognised functional regions within CASK that may represent novel therapeutic targets. By integrating structural modelling, evolutionary analysis, protein dynamics, and ligand-binding site prediction, the student will investigate whether CASK contains cryptic or allosteric pockets that could be exploited pharmacologically. These analyses will generate new hypotheses and provide a foundation for future drug-discovery efforts targeting CASK-associated disorders. The project offers extensive training in computational structural biology, artificial intelligence, bioinformatics, genetics, molecular biology, and quantitative data analysis. Students will gain experience working across both computational and experimental research environments, developing highly transferable skills that are increasingly sought after in academia and industry. Importantly, the student will play an active role in shaping the project's direction. They will help determine which variants and biological mechanisms should be prioritised for experimental investigation and will be encouraged to pursue new questions emerging from their findings such as investigating potential therapeutic targets, or developing improved methods for predicting the impact of disease-causing variants. This flexibility provides an opportunity to make original scientific contributions while advancing our understanding of rare but devastating neurodevelopmental disorders and informing future therapeutic strategies.
Can be completed part time?	Yes
Supervisory Team	
Lead Supervisor	
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Co-Supervisor 3	
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